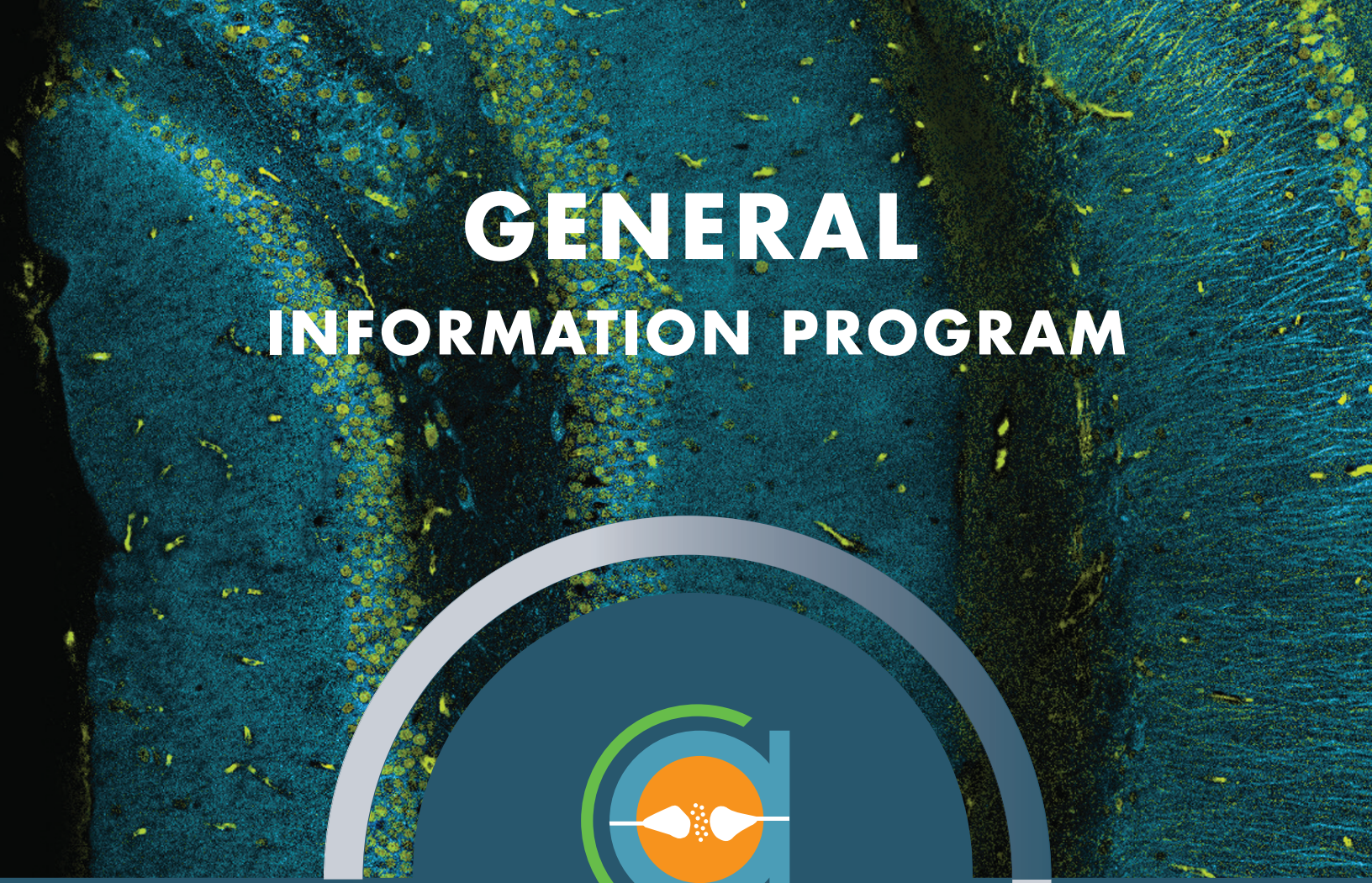

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Title: Galanin(1-15) reverses the impaired long-term memory effect of fluoxetine in the novel object recognition test. Role of 5-HT1A receptor in medial prefrontal cortex

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Abstract: Galanin(1-15) [GAL(1-15)] enhances the antidepressant effects induced by Fluoxetine (FLX) in the forced swimming test through an interaction between GALR1-GALR2 and 5-HT1A receptors in the hippocampus. In this work, we have studied the effects of GAL(1-15) on FLX-mediated effects on the Novel Object Recognition (NOR) and the Object Location Memory (OLM), two tasks where FLX treatment impaired long-term memories 24h post-training. Since the medial prefrontal cortex (mPFC) is a core region for the interaction between emotional processing and cognition with a high density of 5-HT1AR and GALR1 and GALR2, we have also analyzed the binding characteristics and mRNA levels of 5-HT1AR in the mPFC after GAL(1-15)-FLX administration in rats. Groups of male rats (n=5-6) received three injections of FLX(10mg/Kg) between the training and test phases of the NOR and OLM tasks, and a single intracerebroventricular (icv) injection of a threshold dose of GAL(1-15)(1nmol) alone or in combination with the GALR2 antagonist M871(3nmol) 15´ before the test phase. A discrimination index (DI) was calculated as: DI=(N-F)/(N+F), and represent the difference in exploration time expressed as a proportion of the total time spent exploring the two objects. To analyze the binding characteristics and mRNA levels of 5-HT1AR, group of animals (n=6) were injected with FLX(10mg/kg) and GAL(1-15)(1nmol) alone or in combination and coronal sections of the mPFC were obtained to perform a quantitative autoradiography and in situ hybridization experiments In the NOR task, GAL(1-15)+FLX reversed the impairment memory effect induced by FLX(10mg/Kg) ($p<0.05$). This effect was blocked by the GALR2 antagonist M871. On the contrary, GAL(1-15) did not reverse the effect of FLX in the OLM task. In the autoradiographic experiments, GAL(1-15)+FLX increased the Kd ($p<0.01$) and the Bmax ($p<0.05$) values of the agonist radioligand [3H]-8-OH-DPAT compared with FLX in the mPFC. The coadministration also increased the 5-HT1AR mRNA levels ($p<0.01$) compared with the FLX group. Our results describe an interactions between GAL(1-15) and FLX in the mPFC involving interactions at the 5-HT1AR receptor level with implications also at functional level. The GALR1-GALR2-5-HT1A heteroreceptor could be used to reverse some of the adverse effects of FLX on memory processes.

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